REMARKS/ARGUMENTS

This Amendment is responsive to the Office Action dated January 11, 2005. Claims 1-43 were previously pending in the application. Claims 1 – 5, 13 and 19 – 43 have been withdrawn, claims 6 – 12 and 14 – 18 are rejected. By way of this amendment, the Applicant has amended Claims 9 – 12 and 14 - 18.

Claims 6 – 12 and 14 – 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over the teachings of Kniskern et al. in view of Takahashi et al., Essex, and O. Narhi et al. Claims 6 – 12 and 14 – 18 are also rejected under 35 U.S.C. 103(a) as unpatentable over Comberbach et al. in view of Takahashi and Essex.

The Claims are distinguished from the references because the references fail to teach or suggest each element of the recited claims. More specifically, the references fail to disclose or suggest, alone or in combination, the claimed gene, vector, or transformant that causes the expression of the modified pre-S without linkage to the S protein.

The claimed invention relates to a pre-S gene encoding a modified pre-S of HBV, hepatitis B virus (Claims 6 – 8), a recombinant pIL20-pre-S vector with a nucleic acid sequence that codes for mutant pre-S (Claims 9 – 12), and a yeast transformant, where the transformant secretes a mutant pre-S (Claims 14 – 18). The gene, vector, and transformant of the invention code for a pre-S that comprises the whole region of pre-S1 and pre-S2, but that is not linked to the S protein.

Kniskern relates to the expression of the HBV envelope protein having the whole region of pre-S2 and S proteins (the small form of HBV envelope protein). Comberbach relates to the expression of the HBV L protein or modified L protein consisting of the pre-S and S proteins. Thus, both Kniskern and Comberbach teach the expression of proteins that include S proteins, while the claimed gene, vector, and transformant express pre-S without the related S proteins. The remaining references fail to cure the deficiencies of Kniskern or Comberbach, i.e. they do not suggest the modification of Kniskern or Comberbach such that the expression of a pre-S would not be linked with the S protein.

The Claims are also distinguished from the cited references because the results obtained by expression of the pre-S proteins without the S protein are significant and altogether unexpected in view of the references. For the first time, the claimed invention has successfully expressed the pre-S protein without S protein. An adjuvant activity of the recombinant pre-S

protein has been demonstrated, and that activity can be used to improve the immunogenicity of S antigen. The improved immunogenicity is an unexpected benefit over the disclosure of the references. Further, the finding that the replacement of the glycosylation sites of the pre-S with other amino acids, thereby eliminating glycosylation of pre-S, confers the pre-S with an activity that stimulates the immunogenicity of other HBV envelope antigens, rather than an improved immunogenicity of the pre-S itself (see Example 10). The finding that pre-S has an adjuvant activity is not suggested by the references.

The references further fail to teach or suggest the expression of the pre-S protein in a secreted form using a yeast expression system as recited in Claims 14 - 18. The claimed invention demonstrates not only the first successful expression of the recombinant pre-S protein (including both pre-S1 and pre-S2) in secreted form but also the first successful expression of the entire pre-S alone at such a high level (>200 mg/L). The claimed invention enables one to produce the pre-S portion of the HBV envelope protein on a large scale and describes the finding of the utility of pre-S as an adjuvant for the first time.

For the sake of comparison, Applicants attempted to express the L protein in a similar way as in Comberbach, but using the expression system consisting of Saccharomyces cereviciae/pIL20 as recited in Claims 14 – 18. The attempt failed to produce a secreted form of the L protein which was found to be intracellularly expressed as predicted by the Comberbach disclosure. Please refer to the following figure 1 (A: Coomassie blue staining, B: Western blot against anti-HBsAg Ab; lane 1: culture media of recombinant S. cereviciae transformed with pIL-2-pre-S+S gene, lane M: molecular weight marker, lane 2: cell extracts of Hansenula polymorpha transformed with HBV S gene which is a positive control of HBV S antigen). This showing just further demonstrates that Comberbach fails to teach or suggest a secreted protein of any type, much less the pre-S protein contemplated by the invention.

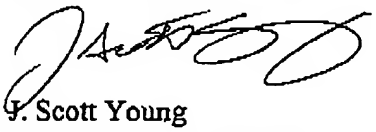
In conclusion, the claimed invention has, for the first time, described the expression of the pre-S protein of HBV, unlinked to the S protein, the expression of pre-S protein using a recombinant pIL20-pre-S vector, and a yeast transformant that expresses a pre-S in the secreted form. The claimed invention has also demonstrated the unexpected function of the recombinant pre-S protein as an immunological adjuvant to stimulate the immunogenicity of S antigen, and the secretion and high expression level of the pre-S protein described in the claimed invention provide the condition for large scale production of the pre-S for industrial purposes. For these

and the other reasons stated above, it is submitted that Claims 6 – 12 and 14 – 16 are patentable over the references, and it is respectfully submitted that the rejections under 35 U.S.C. 103(a) have been overcome.

In view of the amendments and remarks made above, Applicant submits that the pending Claims are now in condition for allowance. Applicant respectfully requests that the claims be allowed to issue. If the Examiner wishes to discuss the application or the comments herein, the Examiner is urged to contact the undersigned by telephone.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,



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Tamara Stevens — April 12, 2005
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